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Treatment of Advanced Prostatic Cancer with Anti-Androgens Alone and a Combination of Anti-Androgen with Anti-Prolactine – A Pilot Study*

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Summary. In this pilot study the treatment of advanced prostatic cancer with cyproteronacetate (Androcur^R) is compared with the treatment of a lower dose cyproteronacetate plus lisuride (Dopergin^R), an anti-prolactin derivative. Treatment was continued until progression and/or the appearance of serious side effects necessitated termination. The duration of the treatment with cyproteronacetate plus lisuride ranged from 2 to 38 months. Most cases showed a partial response, evaluated on the basis of lower levels of prostatic acid phosphatase, relief of bone pain and reduction of bone metastases. Serious side-effects other than impotence did not occur.

Key words: Prostate cancer, Anti-androgens, Anti-prolactin.

Introduction

From the EORTC-Urology Group Study 30761, conducted between 1976 and 1981, which compared treatment with diethylstilboestrol (DES) 3 mg, cyproteronacetate (CPA) 250 mg and medroxyprogesteroneacetate (MPA) 500 mg 1ds, no significant difference exists between DES and CPA in terms of therapeutic efficiency, but CPA had significantly less cardio-vascular side-effects [13]. CPA inhibits the action of 17,20-desmolase and of 3-β-hydroxysteroid dehydrogenase in testosterone synthesis in the Leydig cells and it blocks dihydrotestosterone (DHT)-receptor interaction in the prostatic cells by which translocation of the receptor complex to the nucleus is prevented. CPA however has a stimulating effect on prolactin secretion [10, 11]. Prolactin stimulation by estrogen therapy is well recognised but more recently it has been linked with CPA therapy. Prolactin levels can rise by 2–3 fold [3]; this effect is not seen after orchidectomy. The physiological role of prolactin is in the developement of the female breast (in conjunction with estrogens and gestagens) and on lactogenesis and galactopoiesis [9, 14]. Prolactin acts on the adrenals and testes. There is a synergism between prolactine and LH, measurable by stimulating of LH-receptor binding in Leydig cells [1, 4]. In experiments in rats after hypophysectomy a rise of testosterone levels was observed after administration of prolactin and LH [5]. However a direct action on prostatic cells should be considered as specific prolactin receptors have been found on the membranes of prostatic glandular cells [2]. Drugs with antiprolactin action are bromocryptine, lergotril and lisuride. Bromocryptine has been used in several prostatic cancer trials. We chose lisuride for our pilot study, because it has the same anti-prolactin action as bromocryptine, but in 1/10 of the dosage [6].

Abbreviations. CPA: cyproteronacetate, T: testosteron, DHT: dihydrotestosteron, LH: luteinizing hormone, FSH: follicle stimulating hormone, PSAP: prostate specific acid phosphatase

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Materials and Methods

Seven patients with prostatic cancer, age 60–74 years, were treated with CPA 250 mg daily. Three patients had previous hormonal treatment and another three patients were previously treated with a therapeutic dose of pelvic radiotherapy. Another group of five patients, age 60–82 years, with advanced prostatic cancer was treated with CPA 50 mg t.d.s. plus lisuride 0,2 mg t.d.s. as primary therapy. The following laboratory tests were done before and during treatment: Testosterone (nmol/l), LH (U/l), FSH (U/l), prolactin (U/l) and prostate specific acid phosphatase (PSAP) (U/l). Subjective and objective response were evaluated on the basis of relief of bone pain, decrease of PSAP-levels, decrease of prostatic diameter (by transrectal sonography) and reduction of bone scan lesions.

Progression was noted when an increase in size of the primary tumor was observed or new lesions on the bone scan appeared, usually in conjunction with a rise of PSAP-levels.

When subjective response occurred but no changes in objective parameters (primary tumor and bone-scan) were seen, stable disease was recorded.

Table 1. CPA 5 x 50 mg

No.	Age	Stage	Prev. Th.	Response	Alive/Dead (month)
I	61	$T_0G_2N_xM_1$	R_x; DES	Progr.	48
II	67	$T_3G_3N_xM_1$	R_x; DES	P.R.	50
III	70	$T_3G_3N_xM_0$	Et. oes.	St.	alive (120)
IV	74	$T_{4A}G_2N_xM_0$	Rx	St.	39
V	71	$T_3G_2N_xM_1$	–	Progr.	32
VI	74	$T_3G_3N_xM_0$	–	St.	18
VII	60	$T_3G_3N_xM_0$	–	St.	47

R_x = Radiotherapy; DES = Diethylstilboestrol; Et. oes. = Ethinyloestradiol

Table 2. CPA 3 x 50 mg + Lusurid 3 x 0,2 mg

No.	Age	Stage	Response	Alive/Dead (month)
A	82	$T_3G_2N_xM_1$	P.R.	alive (41)
B	60	$T_3G_2N_xM_1$	P.R.	alive (25)
C	67	$T_3G_2N_xM_1$	Progr.	alive (12)
D	79	$T_3G_3N_xM_1$	P.R.	15
E	76	$T_3G_3N_xM_1$	St.	2

Results

From the seven patients (age 60–74 years) in group I, four were treated with CPA as primary hormonal treatment and three had CPA as second line treatment after having developed cardiovascular side-effects from estrogens. Three patients had primary radiotherapy, after which they showed progression in the form of metastases. Table 1 shows that four patients had stable disease for periods of 18–120 months, one patient had partial response for a period of 27 months and died after 50 months of an unknown cause. Two patients had objective signs of progression after 3 and 8 months, respectively. Two patients died of pulmonary disease and two of natural causes without signs of tumor progression. One patient died of progressive disease and one died of unknown cause.

Serum testosterone levels in all patients treated with 250 mg CPA alone were all below 5 nmol/l (castration level). When progression occurred the PSAP-levels always increased.

Side-effects of CPA-treatment were minimal; princepally gynaecomastia and impotence.

The second group of five patients (60–82 years) with metastatic prostatic cancer was treated with CPA 50 mg tds and lisuride 0,2 mg tds as primary therapy. Duration of therapy until progression or death, was 2–41 months.

Table 2 shows that one patient is still alive and stable after more than 3 years (No. A). Three patients had a partial response, both by objective (transrectal sonography and decrease of PSAP-levels) and by subjective (disappearing of pain and regression of bonescan lesions) assessments. In one patient the bonescan became completely negative after 28 months (No. A). One patient remained stable for 12 months, before progression occurred (No. C). One patient died two months after initiation of therapy from an unknown cause (No. E) and two patients showed progressive disease after 14 and 25 months, respectively (No. D and B).

In all cases of progression a rise of PSAP-levels was seen together with an increase in number of lesions on the bonescan.

Serum testosterone levels (nmol/l) showed considerable variation (Table 3) and in three patients did not reach castrate levels. Serum-LH and serum-FSH also showed individual variations and did *not* seem to be influenced by therapy, as was also observed by Jacobi [7], who used bromocryptine. Prolactin levels in all patients decreased to below the level of detection (0,1 U/l). PSAP-levels decreased to near normal and increased with progression of disease. None of the patients experienced side-effects from the combination anti-androgen plus anti-prolactin in the prescribed dosages, but impotence was reported.

Table 3. CPA 3 x 50 mg + Lisurid 3 x 0,2 mg

No.	Test. (nmol/l)	LH (U/L)	FSH (U/L)	Prol. (U/L)	PSAP (U/L)
A	5–14	7–14	7–21	< 0.1	117 → 3 → 12
B	2.5–5.5	2–5.5	3–4.5	< 0.1	26 → < 3
C	3–10	–	–	0.1	153 → 49 → 159
D	< 2	5–7	3–5	0.15	14 → < 3
E	< 1	–	–	0.1	2 → 0.1

Discussion

Although the number of patients is too small to draw any statistical conclusions, it is probably justified to say, that the combination of low dose anti-androgen + anti-prolactin causes profound prolactin decrease, but that castrate levels of serum testosteron are not achieved.

However the efficacy of treatment in both groups could be regarded as being the same and side-effects were minimal.

The preliminary results of this pilot study are comparable with the results of Jacobi [7], who used 40 mg polyestradiol-phosphate per month i.m. plus 15 mg bromocryptine daily. Jacobi found a pronounced relief of bone pain from osseous metastases combined with a significant improvement in quality of life. In the majority of cases with previously untreated cancer the development of gynaecomastia induced by estrogens and the estrogen-induced hyperprolactinemia was avoided by anti-prolactin treatment. Jacobi observed a partial regression in 24 out of 42 patients, a complete regression in 4 patients evaluated on the basis of the histologically proven reduction of local tumor as well as of bone metastases.

Now that the treatment with LHRH-agonists concerns many clinical trials, there is less scope for large scale trials with combinations of endocrine drugs such as used in this study, however this option does deserve more clinical research as an alternative endocrine treatment.

References

1. Aragona C, Bohnet HG, Friesen HG (1977) Localization of prolactine binding in prostate and testis. The role of serum prolactin concentration on the testicular LH-receptor. Acta Endocrinol 84:402–409
2. Aragona C, Friesen HG (1975) Specific prolactin binding sites in the prostate and testis of rats. Endocrinology 97:677–684
3. Bartsch W, Horst HJ, Becker H, Nehre G (1977) Sex hormone binding globulin binding capacity, testosteron, 5α-dihydrotestosterone, oestradiol and prolactin in plasma of patients with prostatic carcinoma under various types of hormonal treatment. Acta Endocrinol 85:650–664
4. Bohnet HG, Mc Neilly AS (1979) Prolactin: Assessment of its role in the human female. Horm Metab Res 11:533–546
5. Hafier AA, Lloyd CW, Bartke A (1972) The role of prolactin in the regulation of testis function: The synergistic effects of prolactin and luteinizing hormone on the incorporation of [1-^{14}C] acetate into testosteron and cholesterol by testes from hypophysectomized rats in vitro. J Endocrinol 53:223–230
6. Horowski R, Wendt H, Gräf KJ (1978) Prolactin lowering effect of low dose of lisuride in man. Acta Endocrinol 87:234–240
7. Jacobi GH (1980) Palliatiotherapie des Prostatakarzinoms: Endokrinologische Grundlagen, klinische Situation, Prolaktin – ein neues Prinzip. Zuckschwerdt, München
8. Kley HK (1975) Östrogene im Plasma des Mannes, klinisch-experimentelle Untersuchungen. Urban und Schwarzenberg, München Berlin Wien
9. Lobhart A (1978) Klinik der inneren Sekretion, 3. Aufl., Springer, Berlin Heidelberg New York, pp 22–34, 71–134, 286–422, 447–524
10. Mainwaring WIP (1977) Modes of action of anti-androgens: A survey. In: Martini, Motta (eds) Androgens and anti-androgens. Raven Press, New York, pp 151–161
11. Neumann F, Gräf KJ, Hasan SH, Schenck B, Steinbeck H (1977) Control actions of anti-androgens. In: Martini, Motta (eds) Androgens and andi-androgens. Raven Press, New York, pp 163–177
12. Smithline F, Sherman L, Kolodny HD (1975) Prolactin and breast cancer. N Engl J Med 292:784–792
13. de Voogt HJ, Pavone-Maculuso M, Smith Ph, de Pauw M, Suciu B, Sylvester R (in press) Cardiovascular Side-effects of diaethylstilboestrol, Cyproteron acetate, Medroxyprogesterone acetate and Estramustine Phosphate, used for treatment of advanced Prostatic Cancer. Results from trials EORTC 30761 and 30762. J Urol
14. Werder K von (1975) Wachstumshormon und Prolactin-Sekretion des Menschen, Physiologie und Pathophysiologie. Urban und Schwarzenberg, München Berlin Wien

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